201-16171A

Ethane, 1,1'-oxybis-

(Diethyl Ether; CAS RN 60-29-7)

High Production Volume (HPV) Chemical Challenge Final Test Plan and Data Review

Prepared for:

Diethyl Ether Producers Association

Prepared by:

Toxicology/Regulatory Services, Inc.

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TABLE 1: FINAL TEST PLAN

Ethane, 1,1'-oxybis- (Diethyl Ether; CAS RN: 60-29-7)		Information	OECD Study	GLP	Other Study	Estimation Method	Acceptable	Testing Required
STUDY		**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**
PHYSICAL AND CHEMICAL DATA								
2.1	Melting Point	Y	N	N	Y	N	Y	N
2.2	Boiling Point	Y	N	N	Y	N	Y	N
2.4	Vapor Pressure	Y	N	N	Y	N	Y	N
2.5	Partition Coefficient	Y	Y	N	N	N	Y	N
2.6	Water Solubility	Y	N	N	Y	N	Y	N
ENVIRONMENTAL FATE AND PATHWAY								
3.1.1	Photodegradation	Y	N	N	Y	N	Y	N
3.1.2	Stability in Water	Y	N	N	N	N	Y	N
3.3	Transport and Distribution	Y	N	N	N	Y	Y	N
3.5	Biodegradation	Y	N	N	Y	N	Y	N
ECOTOXICITY								
4.1	Acute Toxicity to Fish	Y	N	N	Y	N	Y	N
4.2	Toxicity to Daphnia	Y	N	N	Y	N	Y	N
4.3	Acute Toxicity to Algae	Y	N	N	N	Y	Y	N
TOXICITY								
5.1	Acute Toxicity	Y[1]	N	N	Y	N	Y	N
5.4	Repeated Dose Toxicity	Y[1]	N	Y	Y	N	Y	N
5.5	Genotoxicity *In Vitro* (Bacterial Test)	Y[1]	Y	Y	Y	N	Y	N
5.5	Genotoxicity *In Vitro* (Mammalian Cells)	Y[1]	Y	Y	N	N	Y	N
5.8	Reproductive Toxicity	Y[1]	N	Y	Y	N	Y	N
5.9	Developmental Toxicity / Teratogenicity	Y[1]	N	Y	Y	N	Y	N

[1] Includes data for Dimethyl Ether as an analog.

Ethane, 1,1'-oxybis-
(Diethyl Ether; CAS RN 60-29-7)
High Production Volume (HPV) Chemical Challenge
Test Plan and Data Review

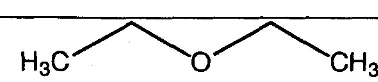
1.0 Introduction

This document reviews the data availability for the High Production Volume (HPV) Chemical Challenge endpoints and provides a proposed test plan for Ethane, 1,1'-oxybis-, hereafter called Diethyl Ether [DEE; CAS RN 60-29-7] for the Diethyl Ether Producers Association. The studies for DEE are summarized in the IUCLID dossier. The members of the Diethyl Ether Producers Association are: Equistar Chemicals, LP (A Lyondell Company) and Hercules Chemical Company.

2.0 General Use and Exposure

Diethyl ether (DEE), as with other unsubstituted ethers, is a very stable industrial solvent. It is most often produced as a by-product of ethanol production. For many years, DEE was used as a human and animal anesthetic although this usage is minimal in more recent times. The use as an anesthetic, however, provides for much of the animal testing designs and knowledge of human exposure. DEE is a good solvent for oils, fats, resins, alkaloids, odorants and dyes. Therefore, it is widely used as a solvent and as an extractant. DEE is used as a reaction medium, due to its low boiling point and solvent properties, for organometallic compounds (i.e. Grignard reagents). DEE also is used as a starter fluid for automotives and in smokeless gun powder.

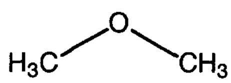
3.0 General Substance Information (Identity)

Chemical Name	Ethane, 1,1'-oxybis-
Synonyms	Diethyl ether 1,1'-Oxybisethane Anaesthetic ether Anesthesia ether Anesthetic ether Diethyl oxide Ethane, 1,1'-oxybis- Ether, ethyl Ethoxyethane Ethyl ether Ethyl ether, tech. Ethyl oxide Solvent ether
CAS Number	60-29-7
Structure	

Molecular Weight	74.12
Substance Type	Organic
Physical State	Colorless liquid
Odor	Sweetish, slightly pungent, characteristic ether

4.0 Analog Justification

Data for Dimethyl Ether (DME; CAS RN 115-10-6) have been used to supplement and fill some HPV Challenge Program endpoints for DEE. The structure of DME is:



DEE and DME[2] are closely related simple ethers with similar physical and chemical properties as well as environmental fate and effects and toxicity profiles. DME is a gas at room temperature with a boiling point of -24.8 °C while DEE is a liquid at room temperature. This difference, however, is of minimal consequence to the environmental fate and effects and toxicity data for the two chemicals because DEE is highly volatile (vapor pressure = 589 hPa) and has a boiling point just above room temperature (34.5 °C). Therefore, DEE will rapidly volatilize under normal circumstances and the primary behavior will be similar to DME gas. For example, the following table summarizes the EPIWIN Suite estimates for fugacity under various release scenarios to the environment for both DEE and DME. The differences are minor, particularly in light of the limited toxicity observed for both chemicals.

Table 2: Comparison of Fugacity Estimates for DEE and DME

Emission Scenario	Percentage distributed to:			
	Air	Water	Soil	Sediment
1,000 kg/hr to Air				
DEE	98%	1.6%	~0.1%	<0.01%
DME	98%	1.5%	~0.1%	<0.01%
1,000 kg/hr to Water				
DEE	4%	95%	<0.01%	~0.1%
DME	10%	89%	<0.1%	~0.1%
1,000 kg/hr to Soil				
DEE	21%	10%	69%	<0.01%
DME	45%	8%	47%	<0.1%

[2] The data for DME have been reproduced as finalized in the HPV Challenge Program submission dated June 26, 2001 with the agreement of the E.I. du Pont de Nemours & Co., Inc. that made the submission (Jepson, 2005).

Table 2: Comparison of Fugacity Estimates for DEE and DME				
	Percentage distributed to:			
Emission Scenario	Air	Water	Soil	Sediment
1,000 kg/hr simultaneously to Air, Water, and Soil				
DEE	16%	65%	19%	<1.0%
DME	33%	54%	13%	<0.1%

5.0 Physical/Chemical Properties

A data summary for DEE is included in Table 3. The Robust Summaries are included in the IUCLID Dataset.

5.1 Melting Point

The melting point for DEE is listed as -116.2 °C (CRC Press, 1975). This value is considered adequate to meet the HPV Chemical Challenge requirements.

5.2 Boiling Point

The boiling point for DEE is listed as 34.5 °C (CRC Press, 1975). This value is considered adequate to meet the HPV Chemical Challenge requirements.

5.3 Vapor Pressure

The vapor pressure for DEE is listed as 589 hPa at 20 °C (DIPPR, 2000). This value is considered adequate to meet the HPV Chemical Challenge requirements.

5.4 Partition Coefficient

The log K_{ow} for DEE was determined in the shake flask method to be 0.82 (Huels, 1988). The EPIWIN Experimental Database (U.S. EPA, 2000a) lists the log K_{ow} as 0.89. These data are considered adequate to meet the HPV Chemical Challenge requirements and indicate that DEE would not be expected to bioaccumulate.

5.5 Water Solubility

DEE is considered to be "slightly" soluble in water with a listed solubility of 65 g/L (CRC Press, 1975). This value is considered adequate to meet the HPV Chemical Challenge requirements.

6.0 Environmental Fate

A data summary for DEE is included in Table 3. The Robust Summaries are included in the IUCLID Dataset.

6.1 Photodegradation

A second order rate of reaction with hydroxyl radicals of 13.3 E-12 cm^3/molecule-sec is reported for atmospheric photodegradation (Atkinson, 1987) that provides a $t_{1/2}$ of 9.8 hours. This value indicates that DEE would be expected to rapidly degrade in the troposphere. These data are considered adequate to meet the HPV Chemical Challenge requirements.

6.2 Stability in Water

DEE, as with other unsubstituted ethers, does not react with water; the only functionality other than carbon-carbon and carbon-hydrogen bonds is the ether linkage (C-O-C) which does not hydrolyze. Therefore, no testing for hydrolysis is proposed.

6.3 Transport and Distribution

The Level III fugacity model (U.S. EPA, 2000b) was used to predict the distribution of a release of DEE to the environment. The high volatility of DEE suggests that the most likely release would be directly to the atmosphere (i.e. 100% to air). For air release, the model predicted a distribution of 98% into atmosphere, 1.6% into water, < 1% into soil and < 0.01% into sediment. Fugacity data for other release scenarios are included in Table 2 in Section 4.0 (above) and in the IUCLID dossier. The available information is considered adequate to support the HPV Chemical Challenge requirements.

6.4 Biodegradability

The biodegradation of DEE was examined using a respirometer test (similar to OECD Guideline 301C). While no specific positive control substance was evaluated, the study was conducted on 78 organic chemicals, many of which were readily biodegradable. In this study, DEE did not degrade to a measurable extent after 240 hours (Urano and Kato, 1986). Similarly, 3 to 7% degradation over 28 days has been reported (CERJI). The lack of biodegradation for unsubstituted ethers (e.g. dimethyl ether) is common. However, it is likely that microbes are capable of utilizing these small molecules as carbon sources. In addition, the high volatility of these ethers may impact the overall measurement of degradation. Therefore, the apparent lack of degradation in these standard tests may reflect the use of the soluble ethers to produce microbial mass without measurable degradation. These data are considered adequate to support the HPV Chemical Challenge requirements.

7.0 Ecotoxicity

A data summary for DEE is included in Table 3. The Robust Summaries are included in the IUCLID Dataset.

7.1 Toxicity to Fish

The 96-hour LC_{50} value for DEE to the freshwater fish, *Pimephales promelas* (fathead minnow), is 2560 mg/L (Geiger *et al.*, 1986). A 14-day LC_{50} value of 2134 mg/L for DEE to the freshwater fish, *Poecilia reticulata* (guppy), is also reported (Koenemann, 1981). For comparison, the 96-hour LC_{50} value for DME is > 4000 mg/L indicating that DEE and DME are relatively non-toxic to fish. These data are considered adequate to support the HPV Chemical Challenge requirements.

7.2 Toxicity to Aquatic Invertebrates

The 24 hour EC_{50} for *Daphnia magna* is reported to be 165 mg/L (Bringmann and Kuehn, 1982). The ECOSAR Model (U.S. EPA, 2000c) provides an estimated 48-hour EC_{50} of 698 mg/L. For comparison, the 48-hour LC_{50} value for DME is > 4000 mg/L indicating that DEE and DME are slightly toxic to relatively non-toxic to aquatic invertebrates. These data are considered adequate to support the HPV Chemical Challenge requirements.

7.3 Toxicity to Aquatic Plants

There are no available data on the toxicity of DEE or DME to aquatic plants; however, the ECOSAR model (U.S. EPA, 2000c) provides an estimated 96-hour EC_{50} value of 410 mg/L for DEE and 1100 mg/L for DME, which is in a range similar to that for fish and daphnia. As described in the Robust Summary for DME, these values are consistent with the body of evidence for ether effects on aquatic plants, were considered adequate for DME within the HPV Chemical Challenge Program and are considered adequate for DEE HPV Chemical Challenge requirements.

8.0 Human Health-Related Data

A data summary for DEE is included in Table 3. The Robust Summaries are included in the IUCLID Dataset.

8.1 Acute Toxicity

The acute oral LD_{50} for DEE in rats was reported to be 1568 mg/kg for 14-day old animals, 1710 mg/kg for young adults and 1211 mg/kg for older animals (Kimura *et al.*, 1971). No standard acute inhalation studies were identified. A series of studies obviously designed to determine the toxicity of DEE related to anesthetic use are included in the IUCLID dossier. In one study, the lethal time for 50% mortality (LT_{50}) was determined for adult and neonatal rats. The results of this study were: LT_{50}: 20 min @ 450 mg/L – adult; LT_{50}: 135 min @ 450 mg/L – neonate; LT_{50}: 17 min @ 605 mg/L – adult; and LT_{50}: 86 min @ 605 mg/L – neonate (Schwetz and Becker, 1971). Two inhalation studies with mice gave 90-minute LC_{50} values ranging from 95 to approximately 200 mg/L (Kobayashi, 1985). This exposure period was selected because it represented the estimated time to peak blood concentration of DEE following anesthesia. For comparison, the 4-hour LC_{50} value for DME exposure to rats was 308 mg/L (164,000 ppm) indicating similar acute toxicity for the two ethers. These data are considered adequate to support the HPV Chemical Challenge requirements.

8.2 Repeated Dose Toxicity

In a 35-day inhalation study with rats, mice and guinea pigs at 1000 or 10,000 ppm (3 or 30 mg/L), the NOAEC was considered to be the highest concentration, 10,000 ppm for rats and 1000 ppm for mice and guinea pigs (Stevens *et al.*, 1975). These studies measured a minimal number of endpoints that included hematocrit and erythrocyte and leukocyte counts for rats as well as body weights, organ weights and histopathology of the liver for all three species. The highest concentration was lethal to mice and guinea pigs and this concentration was terminated at day 20. A 90-day gavage study with rats at 0, 500, 2000 and 3500 mg/kg/day was reported. The top two doses were lethal and the 500 mg/kg was considered a NOAEL (American Biogenics Corp., 1986). Details of this study could not be found. The NOAEC for rats following two years of exposure to DME was 2000 ppm (3.8 mg/L) based on an increase in body weight, a decrease in survival, and/or hemolytic effects in males at 10,000 or 25,000 ppm (DuPont, 1986). These studies confirm the similar toxicity for the two ethers and the feasibility of using DME as an analog for HPV Chemical Challenge requirements for DEE.

8.3 Genetic Toxicity *In Vitro*

DEE has been shown to be negative in the bacterial reverse mutation assay and in an *in vitro* bacterial DNA damage and repair test (De Flora *et al.*, 1984). DME has been shown to be negative in the bacterial reverse mutation assay (DuPont, 2000a) and in a chromosomal aberration assay (DuPont, 2000b). Overall, based on the available data, these two simple ethers would not be expected to be mutagenic *in vivo*. These data are considered adequate to support the HPV Chemical Challenge requirements.

8.4 Reproduction/Developmental Toxicity

A study in mice found no effects on spermatozoa following inhalation exposure to 3200 or 16,000 ppm (9.7 or 48 mg/L) DEE, four hours per day for five consecutive days (Land *et al.*, 1981). An anesthetic dose of DEE (73,000 ppm; 220 mg/L) resulted in early and late abortions and increased variations in fetal mice but the impact of hypoxia cannot be excluded as a potential cause for these effects (Schwetz, 1970; Schwetz and Becker, 1970). In the two-year inhalation study with DME in rats, reproductive organs were examined after 6, 12, 18 and 24 months of exposure (DuPont, 1986). Histopathology of the testes, epididymides, prostate, seminal vesicles, cervix, mammary glands, ovary, uterus and vagina indicated no treatment-related effects up to the highest concentration of 25,000 ppm (47.5 mg/L). In a developmental toxicity study with rats, DME exposures up to 20,000 ppm (38 mg/L) resulted in embryo-fetal toxicity as evident by decreased fetal body weight and an increased incidence of several skeletal variations (DuPont, 1981). At 5000 ppm, one of the skeletal variations observed at the higher concentration was also increased in a concentration-related manner. No teratogenic effects were observed at any exposure concentration. The NOAEC for fetal toxicity was 1250 ppm (2.4 mg/L). Overall, at high concentrations, the simple ethers can result in fetal toxicity that is possibly due to hypoxia and related maternal stress. These data are considered adequate to support the HPV Chemical Challenge requirements for DEE.

9.0 Conclusion

Adequate information is available for melting point, boiling point, vapor pressure, partition coefficient, water solubility, and photodegradation of DEE. Environmental distributions are adequately supported by the appropriate model data. DEE does not have hydrolyzable groups, is stable in abiotic aqueous systems, and is also non-biodegradable in standard laboratory tests. DEE is minimally to relatively nontoxic to fish, daphnia and algae. DEE is relatively non-toxic following acute oral and inhalation exposure. Repeated dose studies indicate no clear target organ toxicity. DEE and DME were not mutagenic in standard mutagenicity assays. DME and, by analogy, DEE are not selective reproductive or developmental toxicants based on available data. The available data for DEE and DME are considered adequate to meet the HPV Chemical Challenge Program requirements for DEE.

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Table 3: Data Summary

Ethane, 1,1'-oxybis-
(Diethyl Ether; DEE)

CAS NO: 60-29-7		SPECIES	PROTOCOL	RESULTS
PHYSICAL-CHEMICAL				
2.1	Melting Point		Handbook Data (CRC)	-116.2 ºC
2.2	Boiling Point		Handbook Data (CRC)	34.5 ºC
2.4	Vapor Pressure		Handbook Data (DIPPR)	589 hPa (at 20 ºC)
2.5	Partition Coefficient (log K_{ow})		Shake Flask Method	0.82
2.6	Water Solubility		Handbook Data (CRC)	Slightly soluble/65 g/L
ENVIRONMENTAL FATE AND PATHWAY				
3.1.1	Photodegradation		Not Stated	Half-life: 9.8 hours (OH Rate Constant)
3.1.2	Stability in Water			Does not react with water; the only functionality other than carbon-carbon and carbon-hydrogen bonds is the ether linkage (C-O-C) which does not hydrolyze
3.3	Transport and Distribution		Level III Fugacity 100% release to air	98% into atmosphere, 1.6% into water, ~ 0.1% into soil, < 0.01% into sediment
			Level III Fugacity 100% release to water	4% into atmosphere, 95% into water, < 0.01% into soil, ~ 0.1% into sediment
3.5	Biodegradation		Similar to OECD 301C	Stable (no degradation in 240 hr)
ECOTOXICOLOGY				
4.1	Acute/Prolonged Toxicity to Fish	*Pimephales promelas*	Similar to OECD 203	LC_{50} (96 hours) = 2560 mg/L
4.2	Acute Toxicity to Aquatic Invertebrates	*Daphnia magna*	DIN 38412	EC_{50} (24 hours) = 165 mg/L
4.3	Toxicity to Aquatic Plants e.g. Algae	Green Algae	ECOSAR v0.99g	EC_{50} (96 hours) = 410 mg/L

Table 3: Data Summary

Ethane, 1,1'-oxybis-
(Diethyl Ether; DEE)

CAS NO: 60-29-7		SPECIES	PROTOCOL	RESULTS
TOXICOLOGY				
5.1.1	Acute Oral Toxicity	Rat		LD_{50} : ~1200 - 1700 mg/kg bw (based on age)
5.1.2	Acute Inhalation Toxicity	Rat	DEE	LT_{50}: 20 min @ 450 mg/L – adult LT_{50}: 135 min @ 450 mg/L – neonate LT_{50}: 17 min @ 605 mg/L – adult LT_{50}: 86 min @ 605 mg/L – neonate
		Mouse	DEE	LC_{50} (90 min) = 95 to ~200 mg/L
		Rat	DME[1]	LC_{50} (4 hr) = 308 mg/L
5.4	Repeated Dose Toxicity	Rat	Inhal (35 days) – DEE	NOAEC = 10,000 ppm (30 mg/L)
			Inhal (2-year) – DME	NOAEC = 2,000 ppm (3.8 mg/L)
		Mouse and Guinea Pig	Inhal (35 days) – DEE	NOAEC = 1000 ppm (3.0 mg/L)
		Rat	Gav (90 days) – DEE	NOAEL = 500 mg/kg
5.5	Genetic Toxicity *In Vitro*			
	Bacterial Test (Gene mutation)	*Salmonella typhimurium*	Ames – DEE/DME	Negative
	DNA Damage/Repair	*E. coli*	Liq micromethod –DEE	Negative
	Chromosomal Aberrations		DME	Negative
5.8	Toxicity to Reproduction / Impairment of Fertility	Rat	Chronic – DME	Negative
5.9	Developmental Toxicity / Teratogenicity	Rat	Dev Tox – DME	NOAEC for fetal toxicity = 1250 ppm No teratogenicity

[1] DME = Dimethyl Ether used as an analog for DEE toxicity.